C. In the Specification

At page 4, lines 23 – 25 delete the following sentence, "The chemical structures of exemplary derivatized carbohydrate useful as stabilizing agents in the formulations of the invention are shown below."

At page 5, please delete lines 1 – 10.

II. REMARKS

Claims 1-22 are pending in the application. New Claim 22 has been added herein. Claims 1, 12 and 20 have been amended herein.

Applicants request that page 5 of the specification be deleted in its entirety. As would be recognized by one skilled in the art, the formulas on page 5 contain inadvertent errors. Applicants contend that these formulas are not necessary to support the term "derivatized carbohydrate" or any particular derivatized carbohydrate. The specification at page 4, lines 20 – 25, page 6, lines 1 – 34 and page 7 lines 1- 25 fully describes the particular derivatized carbohydrates that are useful in the claimed invention.

Example 1 describes the preparation of C8-trehalose. A skilled chemist would easily be able to substitute other fatty acids e.g., palmitic acid, for caprylic acid and obtain other substituted carbohydrates. Also, as would be recognized by the skilled chemist, many derivatized carbohydrates are commercially available as indicated in the specification at page 7, lines 1 –3 and as shown in Table 1 below.

TABLE 1

Derivatized Carbohydrate	**Name**	**Molecular Weight**
C8 – glucose*	n-Octyl-β-D-glucopyranoside	292.4
C9 – glucose**	n-Nonyl-β-D-glucopyranoside	306.4
C10 – glucose*	Decyl-β-D-glucopyranoside	320.4
C12 – glucose**	n-Dodecyl-βB-D-glucopyranoside	348.5
C14 – maltose**	n-Tetradecyl-β-D-maltopyranoside	538.6
* Available from Sigma-Aldrich (www.sigma-aldrich.com)	**Available from Anatrace (www.anatrace.com)	

Accompanying this Response to the Office Action dated August 22, 2002 is a Petition for Extension of Time Under 37 CFR 1.136(a) along with payment of the required fee.

III. The Rejections

A. Rejections Under 35 USC §112, 1st and 2nd Paragraphs.

Claims 1-21 are rejected under 35 USC 112, first paragraph and second paragraph on the grounds that the term "derivatized carbohydrate" is not enabled and that the term renders the claims indefinite.

Claims 20 and 21 particularly claim specific derivatized carbohydrates and thus, it is respectfully asserted that these claims fully comply with Section 112, 1st and 2nd paragraphs.

Independent Claim 1 is amended herein to name particular derivatized carbohydrates using Markush language. It is believed that this amendment obviates Examiner's objection to Claims 1 – 19 under Section 112.

The term "derivatized carbohydrate" is clearly defined in new independent Claim 22 and is fully supported by the specification as discussed in detail under "Remarks" herein.

B. Rejection Under 35 USC §102(b)

Claims 1,3,4,10,11,13, and 18 are rejected under 35 USC 102(b) as being anticipated by US 4,851,211 (Adjei et al.) on the grounds that:

> Adjei teaches an aerosol formulation comprising solvent (ethanol) a lutenizing hormone (protein) suspended in ethanol, and a lipophilic counterion (derivatized carbohydrate). See col. 2, line 7 col. 5 line 51.

Adjei describes an aerosol formulation containing lutenizing hormone releasing hormone (LHRH) and analogs as the active drug substance. Claim 1 and Claim 4 of Adjei are set forth below.

1. An aerosol formulation comprising: a) 0.001-15 mg/g of LHRH analog; b) 0.05-10 mg/g of a lipophilic counterion selected from alkyl ($C_5 - C_{12}$) sulfonic acid or salts thereof; c) 0.1-15% w/w water; d) 0.5-60% w/w ethyl alcohol; and e) q.s. propellant.	4. An aerosol formulation comprising: a) 0.01-2% w/w of a LHRH analog; b) 0.01-2% w/w of a lipophilic counterion selected from alkyl ($C_5 - C_{12}$) sulfonic acid or salts thereof; c) 0.5-50% w/w ethyl alcohol; d) 0.1-15% w/w water; e) 0.05-6% w/w of a surfactant; and f) q.s. propellant.

The formulations taught by Adjei are required to contain a $C_5 - C_{12}$ sulfonic acid/or salts as a "lipophilic counterion". The term "lipophilic counterion" refers to organic acids or their salts with a pka sufficiently low to render them ionizable at the product pH and includes but is not limited to alkyl ($C_5 - C_{12}$) sulfonic acids and salts thereof, palmitates, dioctylsulfosuccinate and its congeners, stearates and salicylates.

Adjei discusses the problems associated with prior art LHRH analogs at col. 1, lines 37-52 and states that:

> LHRH analogs are practically insoluble in fluorocarbons. In mixtures of ethyl alcohol and fluorocarbons, the solubility of leuprolide approaches 3 mg/ml, which is not satisfactory due to dose requirements. This solubility estimate is not significantly affected by the presence of nonionic surfactants because, in part, of solubility and dielectric limitations of such surfactants. In mixtures of fluorocarbons, ethyl alcohol and water, experimental results showed equilibrium solubility of leuprolide to approach 5 mg/ml which is still unacceptable. At high concentrations of ethyl alcohol, a gel-like mass forms resulting in a colloidal dispersion that does not clear at room temperature for up to one month. At water concentrations of 10% or greater, a complete phase separation occurs making a homogeneous formulation impractical and renders aerosolization impractical.

Adjei states that the above described prior art problems are overcome by the inclusion of a lipophilic counterion in the formulations of Adjei which, increases the solubility of LHRH in the formulation (col.5, lines 19-27).

The aerosol formulations of Adjei are required to contain a propellant. The formulation is designed to be filled into an aerosol canister under pressure such as a

metered dose inhaler (MDI). Such aerosol canisters are well known in the art. See US 6,261,539, col. 5 lines 15-19 and US 6,290,930, col. 3 lines 40-45.

The formulations of the present invention contain neither a propellant nor a lipophilic counterion. Further, there is no component in the formulations of Applicants' invention, which is the functional equivalent of either a propellant or a lipophilic counterion. Although Examiner appears to equate a lipophilic counterion with a derivatized carbohydrate, there is nothing in the prior art to suggest such equivalence. The purpose of the lipophilic counterion taught by Adjei is to improve the equilibrium solubility of the LHRH analog in the co-solvent systems described by Adjei. In contrast, the purpose of the derivatized carbohydrate used in the formulations of Applicants' invention is to preserve the biological activity of the protein in the liquid formulations of the invention.

Claims 1,3,4,10,11,13, and 18 are rejected under 35 USC 102(b) as being anticipated by Ban et al. (HU 62473) on the grounds that:

> Ban teaches an aerosol formulation comprising organic solvent (ethanol), an oestrogenic hormone (protein) suspended in ethanol, and -amyl-nitrate (derivatized carbohydrate).

The Ban et al. abstract describes a biocomposition useful to increase erogenous zone sensitivity. The composition may be an ointment or a spray. Dorlands Medical dictionary describes the term "erogenous zone" as follows:

> "a portion of the body stimulation of which produces erotic excitement; such as the genitals, urethra, lips, anus, and breasts." Dorland's Illustrated Medical Dictionary, 25th Ed., 1974, W.B. Saunders, Philadelphia, p. 1745.

Ban discloses a formulation containing the following components:

%w/w	Active Ingredients
0.01-1.0	Isoamylnitrite*
0.01-0.6	Vitamin E or A
0-0.5	Androgenic or Estrogenic Hormones

It is assumed that the compound referred as "isoamylnitrite" is actually isoamyl nitrate; amyl nitrite or isoamyl nitrite is a flammable liquid that forms an explosive mixture with air or oxygen and is incompatible with alcohol. Merck Index 11th Ed., 1989, p. 5013, Merck & Co., Inc., Rahway, N.J., USA. Amyl nitrate is a coronary vasodilator, which is chemically related to nitroglycerin. It is frequently abused as an aphrodisiac and is sometimes referred to by the street name "poppers".

The components in the formulations of Ban are dissolved, emulsified or suspended in various vehicles, e.g., dilute aqueous ethanol, propylene glycol, polyethylene glycol, polypropylene glycol base or an oil soluble ointment base.

The compositions of Ban contain neither a protein nor a derivatized carbohydrate. Estrogen and testosterone can act as hormones but chemically they are steroids not proteins or peptides. Amyl nitrate is neither a carbohydrate nor a protein but a small organic molecule.

Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Found. v. Genentech Inc.*, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991). Neither the Adjei reference nor the Ban reference teaches a composition containing a protein as the active drug substance and a specific derivatized carbohydrate as an essential component for stabilization of the bioactivity of the protein in solution or suspension. Accordingly, neither of these references anticipates Applicants' invention as described by any of the claims presently in the above-identified application.

C. Rejections Under 35 USC §103

Claims 2, 8, 9, 14-17, and 19 stand rejected under 35 USC 103(a) as being unpatentable over Adjei on the grounds that:

> Adjei recites all that is in Claims 2, 8, 9, 14-17, and 19 except for the aerosol comprising the instant amounts of ingredients and instant particle size.

Contrary to Examiner's assertion, Adjei does not recite all that is in Claim 1 and thus, cannot cover all that is in the claims depending from Claim 1. The composition of Adjei is required to contain a propellant and a lipophilic counterion.

Adjei teaches that LHRH analogs are practically insoluble in fluorocarbons. In mixtures of ethyl alcohol and fluorocarbons, the solubility of leuprolide approaches 3 mg/ml, which is not satisfactory due to dose requirements. This solubility estimate is not significantly affected by the presence of nonionic surfactants because, in part, of solubility and dielectric limitations of such surfactants. In mixtures of fluorocarbons, ethyl alcohol and water, experimental results showed equilibrium solubility of leuprolide to approach 5 mg/ml which was still unacceptable. At high concentrations of ethyl alcohol, a gel-like mass formed resulting in a colloidal dispersion that did not clear at room temperature for up to one month. At water concentrations of 10% or greater, a complete

phase separation occurred making a homogeneous formulation impractical and rendering aerosolization impractical.

The problem facing Adjei was getting enough active (leuprolide) in solution without having the composition gel or undergo phase separation. Adjei solved these problems by the addition of the lipophilic counterion to the solvent system.

There is nothing in Adjei, which would point the skilled artisan to the invention claimed herein. The problem solved by Applicants is the preservation of bioactivity over time of a protein or peptide in an aqueous solvent system. Solubility of the protein in the solvent system is not an issue because the biologically active protein may be in solution or suspension.

The claimed invention is directed to a formulation or composition, which is a combination of elements, i.e., a combination of ingredients or compounds. Applicants do not claim to have invented one or more new elements (components) but rather claim a new combination of elements. To support the conclusion that the claimed combination is directed to obvious subject matter, either Adjei must expressly or impliedly suggest the claimed combination or Examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to be obvious in light of the teachings of the reference. *Ex parte Clapp*, 227 USPQ 972, 973 (B.P.A.I. 1985). Based on the arguments presented above it is respectfully asserted that the Adjei reference fails to teach or suggest the formulation of the present invention and that Examiner has failed to present any evidence to the contrary.

The Ban reference describes a conventional ointment or sprayable liquid containing as the active ingredients a mixture of androgens or estrogens, Vitamin E and A and isoamylnitrate. The ointment or spray is useful to stimulate erogenous zones and thus, would be applied topically. There is absolutely no suggestion in the Ban reference that either the ointment or the spray is suitable for inhalation. The composition of Ban does not contain a protein or peptide nor does it contain a derivatized carbohydrate. There is nothing in Ban that would motivate the skilled artisan to modify the compositions of Ban to the extent necessary to arrive at the compositions of the present invention.

Based on the arguments and amendments made herein, it is respectfully asserted that Claims 1 – 22 directed to a stable formulation of a biologically active

protein are in condition for allowance. Examiner is respectfully requested to withdraw the rejections under 35 USC §112, 1st and 2nd paragraphs, 35 USC §102(b), and 35 USC §103(a) and to issue a Notice of Allowance.

Respectfully submitted,

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